Clinical trial results:
A Phase IV, Multicenter, Randomized, Observer-blind, Parallel-arm Study to Evaluate the Safety and Tolerability of CSL's Trivalent Influenza Virus Vaccine (CSL TIV) in Children 5 to Less Than 9 Years of Age.

Summary

EudraCT number	2015-000175-27
Trial protocol	Outside EU/EEA
Global end of trial date	05 December 2014

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	12 June 2015

Trial information

Trial identification

Sponsor protocol code	CSLCT-USF-10-69

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02212106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	bioCSL PTY LTD
Sponsor organisation address	63 Poplar Rd, Parkville, Australia, 3052
Public contact	Clinical Program Director, bioCSL PTY LTD, bioCSL.ClinicalTrials@biocsl.com.au
Scientific contact	Clinical Program Director, bioCSL PTY LTD, bioCSL.ClinicalTrials@biocsl.com.au

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2014
Global end of trial reached?	Yes
Global end of trial date	05 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the frequency and intensity of fever in healthy pediatric subjects 5 to less than 9 years of age administered the 2014-2015 Northern Hemisphere season formulation of bioCSL TIV, in the 7 days after each administration.

Protection of trial subjects:

The Sponsor or its agents submitted the appropriate documents to the local regulatory agencies and IRBs for approval before study start. The principles of informed consent in the Declaration of Helsinki were implemented in this clinical study before protocol specified procedures were carried out. This Phase IV study was conducted as a post marketing study under a United States (US) Investigational New Drug (IND) application and documented in accordance with US guidelines and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 402
Worldwide total number of subjects	402
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	402
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First Patient In: 22-SEP-2014
Last Patient In: 15-OCT-2014
Last Patient Last Visit: 05-DEC-2014
Number of activated sites: 11 (all based in USA).

Pre-assignment

Screening details:

Number of subjects screened: 407
Number of screen failures: 5 (Reason: all due to not meeting inclusion/exclusion criteria).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)

Arm description:

The bioCSL study vaccine is a sterile, thiomersal-free suspension containing 45 mcg total haemagglutinin antigen per 0.5 mL dose (15 mcg each of the three recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season).

Arm type	Experimental
Investigational medicinal product name	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The bioCSL study vaccine is a sterile, thiomersal-free suspension containing 45 mcg total haemagglutinin antigen per 0.5 mL dose (15 mcg each of the three recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season).
Subjects received one or two study vaccinations depending on their influenza vaccine history. The vaccine was administered by intramuscular injection.

Arm title	Comparator Quadrivalent Influenza Virus Vaccine

Arm description:

The comparator vaccine is a US-licensed product containing four recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season.

Arm type	Active comparator
Investigational medicinal product name	Comparator Quadrivalent Influenza Virus Vaccine
Investigational medicinal product code	
Other name	Fluzone® Quadrivalent
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

The comparator vaccine was supplied in a thimerosal free, prefilled syringe containing 60 mcg HA in 0.5 mL (15 mcg of each of the four strains) for each vaccination.
The comparator vaccine is a US-licensed product containing four recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season.
Subjects received one or two study vaccinations depending on their influenza vaccine history. The

vaccine will be administered by intramuscular injection.

Number of subjects in period 1	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)	Comparator Quadrivalent Influenza Virus Vaccine
Started	302	100
Completed	292	96
Not completed	10	4
subject refused the second study vaccination	-	1
Consent withdrawn by subject	2	-
change in family circumstances	1	-
Lost to follow-up	7	3

Baseline characteristics

Reporting groups

Reporting group title	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)

Reporting group description:

The bioCSL study vaccine is a sterile, thiomersal-free suspension containing 45 mcg total haemagglutinin antigen per 0.5 mL dose (15 mcg each of the three recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season).

Reporting group title	Comparator Quadrivalent Influenza Virus Vaccine

Reporting group description:

The comparator vaccine is a US-licensed product containing four recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season.

Reporting group values	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)	Comparator Quadrivalent Influenza Virus Vaccine	Total
Number of subjects	302	100	402
Age categorical Units: Subjects			
Age 5 to < 9 years	302	100	402
Age continuous Units: years			
arithmetic mean	6.7	6.6	
standard deviation	± 1.05	± 1.02	-
Gender categorical Units: Subjects			
Female	147	46	193
Male	155	54	209

Subject analysis sets

Subject analysis set title	bioCSL TIV
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who received at least one scheduled vaccination and had postvaccination follow-up safety data available.

Subject analysis set title	Comparator QIV
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who received at least one scheduled vaccination and had postvaccination follow-up safety data available.

Reporting group values	bioCSL TIV	Comparator QIV	
Number of subjects	292	98	
Age categorical Units: Subjects			
Age 5 to < 9 years	292	98	
Age continuous Units: years			
arithmetic mean			

standard deviation	±	±	

Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)

Reporting group description:

The bioCSL study vaccine is a sterile, thiomersal-free suspension containing 45 mcg total haemagglutinin antigen per 0.5 mL dose (15 mcg each of the three recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season).

Reporting group title	Comparator Quadrivalent Influenza Virus Vaccine

Reporting group description:

The comparator vaccine is a US-licensed product containing four recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season.

Subject analysis set title	bioCSL TIV
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who received at least one scheduled vaccination and had postvaccination follow-up safety data available.

Subject analysis set title	Comparator QIV
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized subjects who received at least one scheduled vaccination and had postvaccination follow-up safety data available.

Primary: The frequency and intensity of fever events occurring during the 7 days after each administration of bioCSL TIV vaccine.

End point title	The frequency and intensity of fever events occurring during the 7 days after each administration of bioCSL TIV vaccine.[1]

End point description:

The overall number of subjects reporting at least one fever event after administration of bioCSL TIV. A fever event was defined as an oral temperature ≥ 38°C (≥ 100.4°F). The intensity was calculated as follows:

- Mild: ≥ 100.4 to < 101.3°F (≥ 38.0 to < 38.5°C)
- Moderate: ≥ 101.3 to < 102.2°F (≥ 38.5 to < 39.0°C)
- Severe: ≥ 102.2°F (≥ 39.0°C)

End point type	Primary

End point timeframe:

7 days after each administration of vaccine.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data were analysed using descriptive statistics only.

End point values	bioCSL TIV			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: Subjects				
Total	24			
Mild	12			
Moderate	6			
Severe	6			

Statistical analyses

No statistical analyses for this end point

Primary: The frequency and intensity of fever events occurring during the 7 days after each administration of bioCSL TIV vaccine.

End point title	The frequency and intensity of fever events occurring during the 7 days after each administration of bioCSL TIV vaccine.[2]

End point description:

The overall percentage of subjects reporting at least one fever event after administration of bioCSL TIV. A fever event was defined as an oral temperature ≥ 38°C (≥ 100.4°F). The intensity was calculated as follows:

- Mild: ≥ 100.4 to < 101.3°F (≥ 38.0 to < 38.5°C)
- Moderate: ≥ 101.3 to < 102.2°F (≥ 38.5 to < 39.0°C)
- Severe: ≥ 102.2°F (≥ 39.0°C)

End point type	Primary

End point timeframe:

7 days after each administration of vaccine.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data were analysed using descriptive statistics only.

End point values	bioCSL TIV			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: percentage of subjects				
number (not applicable)				
Total	8.2			
Mild	4.1			
Moderate	2.1			
Severe	2.1			

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of fever events occurring during the 7 days after each administration of the comparator influenza virus vaccine.

End point title	The frequency and intensity of fever events occurring during the 7 days after each administration of the comparator influenza virus vaccine.

End point description:

The overall number of subjects reporting at least one fever event after administration of the comparator influenza virus vaccine.
A fever event was defined as an oral temperature ≥ 38°C (≥ 100.4°F). The intensity was calculated as follows:
• Mild: ≥ 100.4 to < 101.3°F (≥ 38.0 to < 38.5°C)
• Moderate: ≥ 101.3 to < 102.2°F (≥ 38.5 to < 39.0°C)
• Severe: ≥ 102.2°F (≥ 39.0°C)

End point type	Secondary

End point timeframe:

7 days after each administration of vaccine.

End point values	Comparator QIV			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: Subjects				
Total	9			
Mild	1			
Moderate	4			
Severe	4			

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of fever events occurring during the 7 days after each administration of the comparator influenza virus vaccine.

End point title	The frequency and intensity of fever events occurring during the 7 days after each administration of the comparator influenza virus vaccine.

End point description:

The overall percentage of subjects reporting at least one fever event after administration of the comparator influenza virus vaccine.
A fever event was defined as an oral temperature ≥ 38°C (≥ 100.4°F). The intensity was calculated as follows:
• Mild: ≥ 100.4 to < 101.3°F (≥ 38.0 to < 38.5°C)
• Moderate: ≥ 101.3 to < 102.2°F (≥ 38.5 to < 39.0°C)
• Severe: ≥ 102.2°F (≥ 39.0°C)

End point type	Secondary

End point timeframe:

7 days after each administration of vaccine.

End point values	Comparator QIV			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: percentage of subjects				
number (not applicable)				
Total	9.2			
Mild	1			
Moderate	4.1			
Severe	4.1			

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of vaccine-related fever events occurring during the 7 days after each administration of bioCSL TIV vaccine or comparator influenza virus vaccine.

End point title	The frequency and intensity of vaccine-related fever events occurring during the 7 days after each administration of bioCSL TIV vaccine or comparator influenza virus vaccine.

End point description:

Proportion of subjects with a related fever event (overall) by study vaccine group based on the number of subjects contributing any follow up safety information for at least one data value of an individual sign/symptom. Excludes subjects with missing intensity information for the whole 7 days.
Mild fever: ≥ 100.4 to < 101.3º F (≥ 38.0 to < 38.5º C).
Moderate fever: ≥ 101.3 to < 102.2º F (≥ 38.5 to < 39.0º C).
Severe fever: ≥ 102.2º F (≥ 39.0º C).

End point type	Secondary

End point timeframe:

7 days after each administration of vaccine.

End point values	bioCSL TIV	Comparator QIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292	98		
Units: percentage of subjects				
number (not applicable)				
Total	7.5	5.1		
Mild	4.1	1		
Moderate	1.7	4.1		
Severe	1.7	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of solicited local Adverse Events (AEs).

End point title	The frequency and intensity of solicited local Adverse Events (AEs).

End point description:

The overall frequency and intensity of solicited local Adverse Events (AEs) occurring during the 7 days after each administration of bioCSL TIV or the comparator influenza virus vaccine.
Proportion of subjects who experienced each event are based on the number of subjects in the Safety

Population group. Excludes subjects with missing intensity information for the whole 7 days. Percentages for intensity are based on the number of subjects with non-missing intensity data. Only the maximum intensity experienced between Day 1 and Day 7 are presented for each subject.

End point type	Secondary

End point timeframe:

7 days after each administration of vaccine.

End point values	bioCSL TIV	Comparator QIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292	98		
Units: percentage of subjects				
number (not applicable)				
Total	70.2	68.4		
Total - mild	49.8	46.9		
Total - moderate	17.2	15.3		
Total - severe	3.4	6.1		
Pain - total	64.4	57.1		
Pain - mild	53.3	42.9		
Pain - moderate	9.6	13.3		
Pain - severe	1.7	1		
Redness - total	34.9	37.8		
Redness - mild	26.8	30.6		
Redness - moderate	7.2	3.1		
Redness - severe	1	4.1		
Swelling/Lump - total	29.8	40.8		
Swelling/Lump - mild	21	28.6		
Swelling/Lump - moderate	7.9	8.2		
Swelling/Lump - severe	1	4.1		

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of solicited systemic Adverse Events (AEs).

End point title	The frequency and intensity of solicited systemic Adverse Events (AEs).

End point description:

The overall frequency and intensity of solicited systemic Adverse Events (AEs) occurring during the 7 days after each administration of CSL TIV or the comparator influenza virus vaccine.
Proportion of subjects who experienced each event are based on the number of subjects in the Safety Population group. Excludes subjects with missing intensity information for the whole 7 days.
Percentages for intensity are based on the number of subjects with non-missing intensity data. Only the maximum intensity experienced between Day 1 and Day 7 are presented for each subject.

End point type	Secondary

End point timeframe:

7 days after each administration of vaccination.

End point values	bioCSL TIV	Comparator QIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292	98		
Units: percentage of subjects				
number (not applicable)				
Total	40.8	44.9		
Total - mild	28.4	21.4		
Total - moderate	8.6	19.4		
Total - severe	3.8	4.1		
Headache - total	14.7	23.5		
Headache - mild	11.4	12.2		
Headache - moderate	3.1	10.2		
Headache - severe	0.3	1		
Malaise - total	8.9	14.3		
Malaise - mild	7.2	9.2		
Malaise - moderate	1	5.1		
Malaise - severe	0.7	0		
Muscle ache (myalgia) - total	24.3	23.5		
Muscle ache (myalgia) - mild	20	15.3		
Muscle ache (myalgia) - moderate	3.4	7.1		
Muscle ache (myalgia) - severe	1	1		
Diarrhea - total	5.1	11.2		
Diarrhea - mild	3.8	6.1		
Diarrhea - moderate	1	4.1		
Diarrhea - severe	0.3	1		
Nausea - total	6.8	9.2		
Nausea - mild	5.5	6.1		
Nausea - moderate	0.7	2		
Nausea - severe	0.7	1		
Vomiting - total	2.7	2		
Vomiting - mild	2.1	0		
Vomiting - moderate	0.3	1		
Vomiting - severe	0.3	1		
Fever - total	8.2	9.2		
Fever - mild	4.1	1		
Fever - moderate	2.1	4.1		
Fever - severe	2.1	4.1		

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency and intensity of unsolicited Adverse Events (AEs).

End point title	The frequency and intensity of unsolicited Adverse Events (AEs).

End point description:

The overall frequency and intensity of unsolicited Adverse Events (AEs) occurring during the 7 days after each administration of CSL TIV or the comparator influenza virus vaccine.
Proportion of subjects who experienced each event are based on the number of subjects in the Safety Population group. Excludes subjects with missing intensity information for the whole 7 days.
If a subject has multiple events of the same intensity or causality, then they are counted only once in that intensity or causality. However, subjects can be counted more than once overall.

End point type	Secondary

End point timeframe:

7 days after each administration of vaccine.

End point values	bioCSL TIV	Comparator QIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292	98		
Units: percentage of subjects				
number (not applicable)				
Total	14	22.4		
Total - mild	8.2	12.2		
Total - moderate	5.8	10.2		
Total - severe	0.7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The incidence of Serious Adverse Events (SAEs).

End point title	The incidence of Serious Adverse Events (SAEs).

End point description:

The number of subjects experiencing at least 1 SAE.

End point type	Secondary

End point timeframe:

7 days after each vaccination.

End point values	bioCSL TIV	Comparator QIV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	292	98		
Units: Number of subjects	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

7 days after each vaccination.

Adverse event reporting additional description:

Overall data (following first & second vaccination) for Safety Population is shown.
If a subject has multiple events of the same intensity or causality, then they are counted only once in that intensity or causality. However, subjects can be counted more than once overall

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)

Reporting group description:

The bioCSL study vaccine is a sterile, thiomersal-free suspension containing 45 mcg total haemagglutinin antigen per 0.5 mL dose (15 mcg each of the three recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season).
Subjects received one or two study vaccinations depending on their influenza vaccine history.

Reporting group title	Comparator Quadrivalent Influenza Virus Vaccine

Reporting group description:

The comparator vaccine is a US-licensed product containing four recommended influenza strains for the Northern Hemisphere 2014/2015 influenza season.
Subjects received one or two study vaccinations depending on their influenza vaccine history.

Serious adverse events	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)	Comparator Quadrivalent Influenza Virus Vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 292 (0.34%)	0 / 98 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Delirium febrile			
subjects affected / exposed	1 / 292 (0.34%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	bioCSL Trivalent Influenza Virus Vaccine (bioCSL TIV)	Comparator Quadrivalent Influenza Virus Vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	222 / 292 (76.03%)	75 / 98 (76.53%)	
Nervous system disorders			
Headache			
subjects affected / exposed	43 / 292 (14.73%)	23 / 98 (23.47%)	
occurrences (all)	55	32	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	188 / 292 (64.38%)	56 / 98 (57.14%)	
occurrences (all)	230	71	
Redness			
subjects affected / exposed	102 / 292 (34.93%)	37 / 98 (37.76%)	
occurrences (all)	117	44	
Swelling / Lump			
subjects affected / exposed	87 / 292 (29.79%)	40 / 98 (40.82%)	
occurrences (all)	101	50	
Malaise			
subjects affected / exposed	26 / 292 (8.90%)	14 / 98 (14.29%)	
occurrences (all)	32	18	
Fever			
subjects affected / exposed	24 / 292 (8.22%)	9 / 98 (9.18%)	
occurrences (all)	25	11	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	15 / 292 (5.14%)	11 / 98 (11.22%)	
occurrences (all)	19	16	
Nausea			
subjects affected / exposed	20 / 292 (6.85%)	9 / 98 (9.18%)	
occurrences (all)	22	9	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	71 / 292 (24.32%)	23 / 98 (23.47%)	
occurrences (all)	80	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2014	Protocol amendment 1 Final Version 2.0, included the following changes: • Update the tertiary objective/endpoints to secondary objectives/endpoints (safety and tolerability after vaccination with test and comparator vaccines). • Clarified that if multiple temperatures readings are taken, the maximum reading for each day should be recorded. • Added prophylactic antipyretics on the day of vaccination to prohibited medicines section.
02 May 2014	Protocol amendment 2 Final Version 3.0, included the following changes: • Change in terminology of comparator group from Comparator Influenza Virus Vaccine to Comparator Trivalent Influenza Virus Vaccine (TIV) • Change in the enrollment halting rules
05 August 2014	Protocol amendment 3 Final Version 4.0, included the following changes: • Addition of PI and Sponsor details, number of treatments, text in dosage and administration section.
04 September 2014	Protocol amendment 4 Final Version 5.0, included the following changes: • Corrections and additions of text from Comparator TIV to Comparator QIV. All subjects enrolled to the trial were enrolled under this amendment (version 5). Note: The sponsor, bioCSL, was previously known as CSL Biotherapies. It should therefore be noted that, in the study documents (including the protocol and statistical analysis plan) bioCSL TIV is referred to as CSL TIV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported